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CURRENT PROGRESS

Clinical Significance of Urinary LDH, Alkaline Phosphatase and Other Enzymes

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REPORTS which include studies of one or more urinary enzymes now number over 200; many have related enzyme activity to disorders of the urinary tract and in this regard lactic acid dehydrogenase (ULDH) has been most studied.[1-50] Alkaline phosphatase (UAP),[1, 2,17,18, 21, 29, 34, 51-59] β-glucuronidase,[60-75] lysozyme,[21, 76-84] acid phosphatase[52, 85-89] and catalase[6, 90-99] have also received appreciable investigation, whereas transaminase[6] and leucine aminopeptidase[100-102] have attracted less attention. There have been several studies of urinary amylase[103, 104] and lipase,[105] but these have been concerned chiefly with the diagnosis of pancreatitis. Three editorials on this subject[106-108] have appeared. Numerous studies of the above and other urinary enzymes, including aldolase, butyric esterase, diamine oxidase, hyaluronidase, ribonuclease, sulfatase and urokinase, were reviewed in 1962 by King and Boyce;[109] 150 references are listed.

Several optimistic claims for the value of urinary enzyme assays as aids in the diagnosis or localization of disorders of the urinary tract have been made, some of which follow.

ULDH activity has been reported to be elevated in patients with malignant tumours of the kidney, bladder and prostate, and UAP activity is said to be increased with neoplasms of the kidney and prostate, but not of the bladder unless invasion of muscle has occurred.[1, 2] Indeed, it has been predicted that the widespread use of ULDH assay as a screening procedure would greatly increase the rate of detection of early carcinomas and lead to a significant reduction in their lethality.[107] Estimation of acid phosphatase has been proposed as an aid in the diagnosis of carcinoma of the prostate[86, 89] and β-glucuronidase as a possible factor in the genesis of bladder neoplasms;[62] in fact, an increase in urinary β-glucuronidase activity of a worker in the chemical industry exposed to a bladder carcinogenic hazard has been suggested as an indication that his work place should be changed, even if no neoplasm can be demonstrated.[66]

In chronic pyelonephritis, ULDH has been reported to be elevated whereas UAP activity was seldom found increased.[2] Elevation of β-glucuronidase has been said to indicate pyelonephritis rather than infection of the lower urinary tract,[61] and catalase activity has been suggested as a simple rapid aid in the diagnosis of bacteriuria, especially in persons with hypertension.[97] Both catalase and β-glucuronidase have been reported sometimes to indicate renal injury from pyelonephritis, even when bacteriuria is absent.[72]

ULDH has been proposed as an aid in determining the cause of hypertension, since it has been found normal in benign essential hypertension and frequently elevated when hypertension is secondary to renal parenchymal disease.[50]

ULDH assay has been suggested as a useful screening test of renal disease, especially in the presence of a normal urinary sediment.[33] Serial measurements of ULDH and UAP have been considered particularly useful in evaluating the course and type of glomerulonephritis.[2] ULDH, UAP and lysozyme have been suggested as aids in the diagnosis of kidney transplant rejection.[29, 37, 80] Lysozyme excretion was found particularly suitable for the clinical diagnosis of impaired renal tubular function,[78] and urinary concentrations of both lysozyme and ribonuclease have been reported as valid estimates of "tubular proteinuria".[78] Catalase has been proposed as a useful screening test for abnormal urine,[91] and release of catalase from the cells of the renal tubules has been quoted as being probably the most sensitive index of renal damage.[94] Acid phosphatase in ureteral urine has been suggested as a test for unilateral renal disease.[88] Finally, the diagnostic sensitivity of elevated urinary en-

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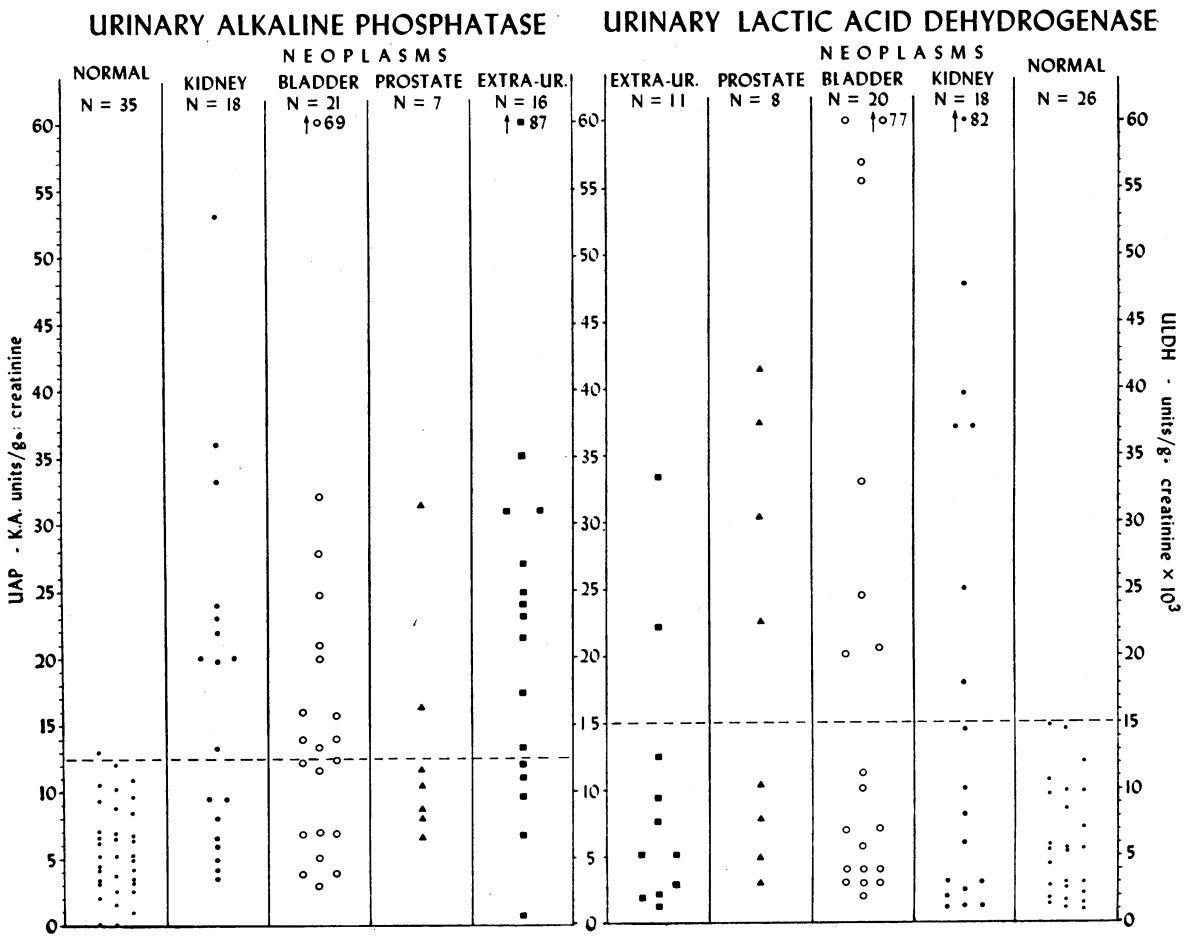

Fig. 1.—Activity of urinary lactic acid dehydrogenase and alkaline phosphatase in patients with neoplasms of the kidney, bladder and prostate, compared with values found in patients with extra-urinary neoplasms and in healthy subjects. (Reproduced by kind permission from *Brit. J. Urol.*, 39: 294, 1967.)

zymes (ULDH, UAP) has been said to permit the diagnosis of early renal and urological disease before irreversible renal damage has occurred.[2]

It is our purpose to evaluate these claims in relation to other reports and to our own studies of ULDH and UAP.

Materials and Methods

ULDH and UAP were determined by methods previously described.[18] One hundred and twenty-five assays for ULDH and UAP were performed on eight-hour overnight urine collections in normal controls and in 62 patients who had neoplasms; 10 of the latter had determinations on more than one occasion and one patient had serial determinations for 11 days. Urine samples used for other assays were aliquots of first morning specimens. Analyses included 230 from 61 patients with glomerulonephritis, pyelonephritis and hypertension and 2000 from 30 patients who had received cadaver kidney transplants. In addition to the patients with transplants, all of whom had serial values determined daily for at least the first 30 days, 41 of the 61 patients with medical disorders involving the kidney had enzyme determinations performed on urine collected on two or more separate days. Eleven of the 41 had 6 to 20 determinations, usually with three or more consecutive days included.

Twenty-one patients suffered from carcinoma of the bladder, eight from malignancy of the prostate and 18 from renal carcinoma; these have been reported previously,[18] except for five additional patients with carcinoma of the kidney. Diagnoses were confirmed histologically at the time of operation or autopsy in all patients with neoplasms, and by renal biopsy in the 16 patients with glomerulonephritis; 11 of the latter had chronic proliferative or combined membranous and proliferative lesions, two had membranous glomerulonephritis and in three, acute proliferative lesions were subsiding. All 10 patients

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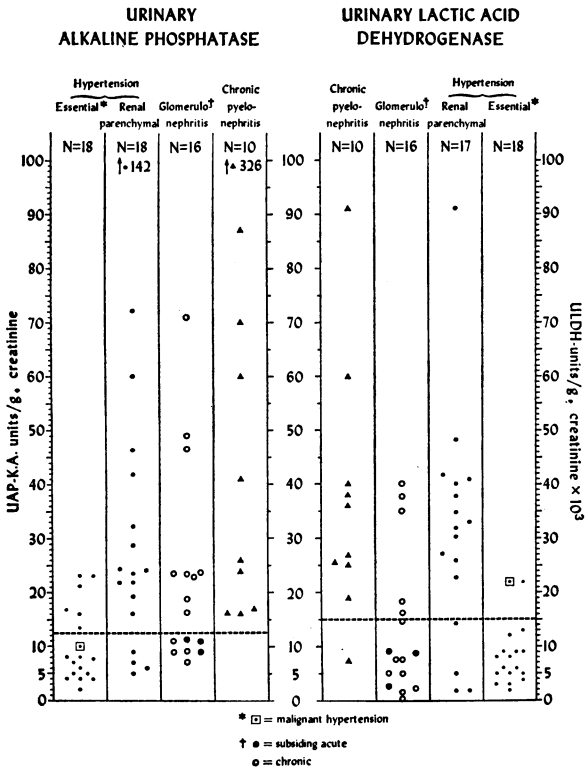

Fig. 2.—Activity of urinary lactic acid dehydrogenase and alkaline phosphatase in patients with essential hypertension, hypertension associated with renal parenchymal disease, glomerulonephritis and chronic pyelonephritis.

considered to have chronic pyelonephritis had 30 or more leukocytes per high-power field on urinalysis, bacteria seen on a gram-stained smear of uncentrifuged mid-stream urine and at least three cultures collected at intervals over a period of several months showing a heavy bacterial growth; symptoms referable to infection were absent at the time of study.

Criteria for the diagnosis of essential hypertension in our group of 18 patients included normal urinalysis and intravenous pyelography, bilaterally symmetrical ^{131}I hippuran renogram and ^{203}Hg chlormerodrin scan, and sterile urine culture; renal arteriography was normal in all eight patients on whom this test was performed. Diastolic blood pressures averaged 100 to 110 mm. Hg in the majority of cases. The 18 patients considered to have hypertension secondary to renal parenchymal disease were drawn from the groups with glomerulonephritis and pyelonephritis, except for seven patients; three of the latter had polycystic disease and two had sustained recent renal infarctions.

The diagnosis of rejection in the 30 patients who had received cadaver kidney transplants was made using criteria previously reported.[110]

RESULTS

Results are presented in Figs. 1 and 2. When determinations were made on urine collected on more than one day from a given patient, mean values were used; in this group 56% had UAP and 33% had ULDH values recorded in both normal and abnormal ranges, indicating that wide day-to-day variation in urinary activity is common for these enzymes.

The frequency of elevated values in patients with neoplasms of the urinary tract in this series is compared with that reported by others in Table I for ULDH and in Table II for UAP.

Neoplasms of the Urinary Tract (Fig. 1)

Urinary alkaline phosphatase activity was elevated in 55 and 57% of patients with neoplasms of kidney and bladder respectively, compared with an elevation of ULDH in 40% of cases with each type of tumour. UAP was increased in two of seven and ULDH in four of eight patients with carcinoma of the prostate. UAP activity was raised in 68% of 18 patients with extra-urinary malignant neoplasms and elevations occurred in this group when the activity of serum alkaline phosphatase was either normal or elevated. ULDH activity was, however, elevated in only two of 11 patients with extra-urinary carcinomas.

Pyelonephritis, Glomerulonephritis and Hypertension (Fig. 2)

Activity of both UAP and ULDH was almost invariably elevated in this group of patients with chronic pyelonephritis. UAP was elevated in the majority of patients with chronic glomerulonephritis (69%) and ULDH somewhat less frequently (38%). The results in patients with benign essential hypertension were in marked contrast to those in patients with hypertension associated with renal parenchymal disease, particularly in regard to ULDH, which was increased in 13 of 17 of the latter, compared with one of the 17 with benign essential hypertension.

Kidney Transplant Rejection

Results of daily UAP and ULDH assays obtained during transplant rejection episodes demonstrated an increase in activity of one or both enzymes in many instances; however, activity failed to increase with some major rejection episodes and elevated activity occurred at times in the absence of significant demonstrable rejection. These findings will be reported in detail elsewhere.

We have found little evidence to support the suggestion that patterns of UAP and ULDH

TABLE I.—ULDH IN NEOPLASMS OF KIDNEY AND BLADDER

	Carcinoma of kidney		*Carcinoma of bladder*		*Carcinoma of prostate*	
	No. of cases	*No. with activity increased*	*No. of cases*	*No. with activity increased*	*No. of cases*	*No. with activity increased*
Wacker and Dorfman,[49] 1962	6	5	13	13	—	—
Amador, Zimmerman and Wacker,[1] 1963	17	16	14	14	—	—
Riggins and Kiser,[39] 1963	4	4	—	—	14	11
Macalalag and Prout,[31] 1964	8	8	—	—	—	—
Ramkissoon *et al.*,[38] 1964	2	0	4	3	—	—
Appert,[4] 1965	—	—	26	9	5	2
Böttiger, Lindstedt and von Schreeb,[5] 1966	17	12	6	5	—	—
Colbert, Carrera and Kittredge,[7] 1966	8	7	20	12	6	3
Deliveliotis *et al.*,[10] 1966	11	8	7	7	5	0
Dubach and Padlina,[55] 1966	7	6	—	—	13	10
Emerson and Morgan,[15] 1966	3	2	17	13	1	1
Goldberg, Chakrabarti and Filipich,[21] 1966	3	1	2	2	—	—
Kiser and Riggins,[27] 1966	8	6	14	12	8	4
Lee *et al.*,[30] 1966	19	16	—	—	—	—
Mirabile, Bowers and Berlin,[32] 1966	7	6	15	11	8	7
Gault *et al.*,[18] 1967	18	7	20	8	8	4
Schwartz and Grabstald,[48] 1967	—	—	99	53	—	—
Total	138	104 (75%)	257	162 (63%)	68	42 (62%)

activities are of appreciable diagnostic value[2] in nephrological or urological disorders, and are in agreement with the conclusion of Dubach and Padlina[55] that a combined increase in activity of these two enzymes in urine does not possess additional diagnostic significance.

DISCUSSION

Problems Related to Enzyme Assay and Expression of Activity

Accurate assay of several enzymes, including ULDH and UAP, is made more difficult by the relatively low normal activity in urine as compared to serum.[18] Inhibitors are common;[11, 47, 57, 59, 67, 70, 109] they may not always be completely removed by dialysis[56, 59, 67, 68, 111] and may vary in activity with urine flow rate or dilution[73] and with storage in the cold.[56] Activators may be lowered to suboptimal concentration by dialysis[73] and it will probably be found that there are drugs which interfere with assays.

Enzyme activity in serum is ordinarily expressed per standard volume. Unfortunately, variation in flow rates may make this method inaccurate when applied to urine. Many studies have therefore utilized timed urine collections of eight hours or more; however, such collection periods may provide increased time for release of enzyme such as LDH from erythrocytes or leukocytes, may require cooling of the specimen and are also subject to the volume and timing errors which are so difficult to avoid under standard ward conditions. We have preferred expression of activity as units per gram of creatinine, using a freshly voided morning specimen, which will usually be concentrated to a variable extent. A comparable method of expressing activity has been used by others.[5, 61, 70, 73] Although subject to some limitations, we have found that values derived in this manner agree closely with those expressed as units per timed volume,[18] as did Böttiger, Lindstedt and von Schreeb.[5]

Problems in Interpretation of Results

Many variables must be considered when results are interpreted, including the several possible sources of enzymes found in urine.[45] Most recent studies indicate that increased

TABLE II.—UAP IN NEOPLASMS OF KIDNEY AND BLADDER

	Carcinoma of kidney		*Carcinoma of bladder*		*Carcinoma of prostate*	
	No. of cases	*No. with activity increased*	*No. of cases*	*No. with activity increased*	*No. of cases*	*No. with activity increased*
Amador, Zimmerman and Wacker,[1] 1963	17	15	14	3	—	—
Dubach and Padlina,[55] 1966	7	2	—	—	13	5
Gault *et al.*,[18] 1967	18	9	21	12	7	2
Total	42	26 (62%)	35	15 (43%)	20	7 (35%)

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ULDH values may arise from erythrocytes or leukocytes,[18, 19, 32, 39, 43, 45] and the problem of distinguishing enzyme activity arising from urinary tract tissue or neoplasms, as distinct from red and white blood cells, has been highlighted by the study of Gelderman, Gelboin and Peacock;[19] these authors found the LDH isozyme pattern of urine from patients with carcinoma of the bladder to resemble that of the formed elements of the urinary sediment rather than that of the tumours. Bacteria may produce ULDH[43, 45] as well as β-glucuronidase[108] and catalase,[81] and enzymes may have their source in seminal or prostatic fluid.[45, 112] Urine collected from intestinal conduits[45] and urinary fistulas may have high enzyme values owing to an extra-urinary source of enzyme such as the intestine; our highest recorded values for UAP have been in such patients, including one in whom urine values were persistently higher than in serum. Increased activity may also occur after instrumentation of the urinary tract in the case of ULDH[49] and during pregnancy for UAP[55] and β-glucuronidase;[71] activity of the latter enzyme may also be increased following major operations on the alimentary tract or fractures, and in association with fever or cortisone therapy.[74]

It may be difficult to distinguish enzyme activity arising from urinary tract tissue from that originating in plasma. This may be a problem, as is the case with alkaline phosphatase[18, 51] and lysozyme[84] when plasma activity is elevated, when permeability of the glomerular filtration apparatus is increased, when tubular damage leads to decreased reabsorption[77, 78] or when there is leakage through damaged capillaries anywhere in the urinary tract. There is evidence that alkaline phosphatase,[18, 51, 55] β-glucuronidase,[71, 74] LDH[7] and lysozyme[84] may all appear in increased amounts in urine in the absence of detectable disease of the urinary tract, presumably from plasma. Current knowledge concerning the origin of enzymes in urine and their distribution and relative activities in different parts of the kidney have been reviewed by Mattenheimer.[113, 114]

An additional important variable suggested by both this and other studies is the wide day-to-day variation which may occur in the activity of urinary enzymes such as ULDH,[18] UAP[18, 53, 55] and β-glucuronidase.[73] There is also evidence to suggest some diurnal variation in the excretion of UAP,[55] ULDH[12] and β-glucuronidase[73] and an effect of acid-base status on β-glucuronidase.[73]

It is not surprising that different authors have reported conflicting results, considering the numerous physical and chemical factors which may vary widely in urine and complicate assay of enzymes, and the many problems which make it difficult to interpret the values obtained; variation due to differences in methods of enzyme estimation would appear to be of lesser importance in most instances. The observation that many variables are difficult to control necessitates that one should be careful not to attach too much significance to small differences in urinary enzyme activity.

Studies of Urinary Enzymes in Specific Disorders of the Urinary Tract Neoplasms

Neoplasms.—Review of several studies (Table I) indicates that ULDH has been found increased in 75% of 138 patients with malignant neoplasms of the kidney, in 63% of 257 patients with carcinoma of the bladder and in 62% of 68 patients with carcinoma of the prostate. UAP has been found increased in 62% of 42 patients with malignant neoplasms of the kidneys, in 43% of 35 such lesions of the bladder and in 35% of 20 patients with carcinoma of the prostate (Table II). Thus UAP activity may be elevated, although somewhat less frequently than ULDH, in these three malignant urinary tract tumours and in non-invasive neoplasms of the bladder.[18, 55] It is also clear that malignant tumours from any of these three sites may be present with normal ULDH or UAP values (Tables I and II), irrespective of method used for assay;[7, 18, 27, 43, 55] our results suggest that this is particularly true with small localized tumours,[18] and normal values of ULDH have been found when growth of the neoplasm has resulted in an autonephrectomy.[10]

In addition to the problem of inappropriate negative values, the many possible causes of increased ULDH and UAP activity markedly reduce the significance of elevated values in patients suspected of urinary tract neoplasm. Noteworthy are reports of increased UAP activity in association with increased serum values[18, 51] and also with extra-urinary neoplasms;[18] ULDH values have been reported elevated in an appreciable number of patients with renal cysts[7] and also in the presence of extra-urinary malignant neoplasms.[7] Our studies suggest that ULDH activity is less commonly elevated by extra-urinary neoplasms than is UAP (Fig. 1), and agree with others that ULDH has little relationship to serum activity.[7, 49]

Macalalag and Prout[31] concluded that the isoenzyme pattern of LDH in urine reflected the

pattern in kidney tumour tissue (increased isoenzymes IV and V, i.e. slowly migrating fractions) and might be helpful in distinguishing cyst from tumour. Dubach,[13] however, found the urinary isoenzyme pattern to depend more on the predominant type of blood cell present than on the disease, and patients with neoplasms have been reported without significant increase in fractions IV and V in urine.[7] An increase in ULDH isoenzyme V has also been reported in non-neoplastic kidney diseases.[24] Nevertheless, a study of isoenzymes may contribute more than has the study of total activity.

In 1955 Boyland, Wallace and Williams[62] reported high β-glucuronidase activity not only in bladder tumour tissue and associated urine, but also in the mucosa surrounding the tumour and in urine after surgical removal of such tumours. These findings led them to speculate that this enzyme might act as a trigger mechanism, precipitating the development of tumour by releasing an active carcinogenic agent from an inactive glucuronide. The appearance of some supportive evidence followed,[66] and it appears that most malignant bladder tumours are associated with increased urinary excretion of β-glucuronidase.[62, 64, 65, 69, 74, 75] Nevertheless, increased activity in urine clearly occurs in several other disorders,[61, 71, 74, 108] including a damaged bladder mucosa[65] and renal and extra-urinary neoplasms.[69] Such elevations may equal or even exceed in degree those found with carcinoma of the bladder. Other investigators have not been able to confirm that increased activity regularly persists after surgical removal of bladder tumours,[60, 64] and Appert and Richterich[60] also found that increased activity occurred only coincident with and not preceding development of vesical new growth. It therefore seems unlikely that increased activity of β-glucuronidase contributes to the genesis of bladder cancer.

Urinary acid phosphatase has failed to prove an aid in the diagnosis of carcinoma of the prostate.[85, 87]

The evidence does not suggest that assay of the urinary enzymes studies to date adds anything of major importance to established techniques of investigation of urinary tract tumours, considering the important number of false negatives and the many causes of increased activity. However, increased urinary enzyme activity has been reported in a significant number of patients with urinary tract neoplasms in whom there was no abnormality of the urinary sediment,[5, 18] and further studies to establish the frequency of this finding seem warranted.

Pyelonephritis.—The initial suggestion that assay of urinary β-glucuronidase would help to distinguish bacterial infection of the kidney from that of the lower urinary tract[61] seems unlikely to be correct.[71, 108]

We have been unable to confirm the observation that elevated ULDH occurs in the presence of normal UAP activity in chronic pyelonephritis;[2] all our patients with this disorder had increased UAP activity (Fig. 2). Conclusions are limited, however, to patients with 30 or more leukocytes per high-power field and high-grade bacteriuria, and we have no indication as to what might be found in more indolent or occult forms of this disorder.

Catalase estimation appears to be of limited value as a screening test for infections of the urinary tract because of the lack of specificity and an important number of false negatives;[6, 91, 95] nevertheless, good results have been reported.[96]

Limited data suggest that total urinary LDH activity may be increased in an appreciable number of cases of pyelonephritis when there is no significant abnormality of the urinary sediment;[33] also that catalase and β-glucuronidase may indicate renal injury from pyelonephritis, even when bacteriuria is absent.[72] However, total ULDH has been reported as possessing no advantage over a thorough urinalysis,[43] and confirmation of these suggestions is necessary.

Glomerulonephritis.—We have not found support for the conclusion that serial measurements of ULDH and UAP are particularly useful in evaluating the course and type of glomerulonephritis.[2]

Hypertension.—We have some confirmatory evidence (Fig. 2) for the suggestion that ULDH is normal in benign essential hypertension and is frequently elevated when hypertension is secondary to renal parenchymal disease;[33, 50] however, it has yet to be demonstrated that assay of this enzyme provides more information relevant to the diagnosis of hypertension than does a careful urinalysis. Some patients with benign essential hypertension had slight elevations of UAP activity (Fig. 2), in contrast to our findings for ULDH.

Kidney transplant rejection.—Extensive study of ULDH and UAP after transplantation of the kidney in humans[115] has not borne out our original optimism that assay of these enzymes might provide a consistently reliable aid in the diagnosis of rejection.[29] Normal values in the presence of some severe rejection episodes, lack of specificity of increased activity and failure of the degree of elevation to correlate with the severity of rejection have proved to be the greatest drawbacks. We believe that studies in

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depth in this situation, considering all types of rejection episodes, will probably result in similar findings for other enzymes. Nevertheless, serial assays of ULDH, UAP and perhaps lysozyme,[80] when limitations are recognized, may provide significant assistance in the diagnosis of rejection. We also have some evidence[115] which suggests that rejections chiefly manifested by mononuclear cell infiltration are more frequently associated with increased ULDH and UAP activity than those manifested predominantly by vascular abnormalities, and it is possible that urinary enzyme determinations may help distinguish rejection types.

Renal tubular disorders.—High values for urinary lysozyme activity have been obtained in humans with the Fanconi syndrome[78] and those exposed to cadmium[76, 78] and also in rats after administration of agents toxic to the proximal tubule.[77] Thus lysozyme activity may find a useful place in the diagnosis of impaired renal tubular function[78, 81] and may be taken as a valid estimate of tubular proteinuria.[78] Nevertheless, increased lysozyme activity is clearly not specific for tubular disorders, having been reported in association with glomerulonephritis and proteinuria,[78] with renal failure due to various causes[78, 81] and when serum values are considerably elevated owing to leukemia in patients without clinical evidence of renal disease.[116] There appears to be a renal threshold for excretion of this enzyme, and when serum values exceed this threshold, urinary values will no longer be a useful index of tubular injury.[116]

CONCLUSIONS

The wide variations in many physical and chemical factors in urine and its flow rate, the frequent major day-to-day fluctuations in excretion of some enzymes, the important influence of activators and inhibitors and the several possible sources of urinary enzymes, all lead to difficulty in obtaining accurate assays and in the interpretation of results. The many variables require evaluation for each enzyme, if optimal assay conditions are to be obtained and if results are to be meaningful.

The initial optimism that assay of various enzymes in urine would prove to be an important aid in specific diagnosis or localization of disease of the urinary tract has to date unfortunately proved excessive. In most instances definitive suggestions have been found unwarranted by subsequent studies or remain unconfirmed. False negatives and lack of specificity are major problems, and few studies have demonstrated an appreciable advantage over standard urinalysis. One cannot yet propose a clear-cut and important place for the determination of urinary enzymes in clinical urology or nephrology, although restricted areas of value may be suggested, and an evaluation of isoenzyme patterns may contribute more than assay of total activity. More studies are required to determine the incidence with which activity of various enzymes is increased in the early stage of urinary tract disease and when there is little or no abnormality on urinalysis. Should such studies demonstrate a useful role, which might be in the form of a non-specific indicator of urinary tract disorder supplementing urinalysis, automated methods, such as are already available for LDH and alkaline phosphatase, could make such tests possible on a routine screening basis at a relatively small cost to the patient. Indeed, in the future a battery of tests, including those for certain enzymes, perhaps selected from the point of view of their relative activities in different parts of the nephron and cellular microanatomy, could be done simultaneously on a small sample of urine using automated equipment, as is being done to an increasing degree for screening purposes on blood.

Summary Some suggestions that assay of enzymes in urine, including urinary lactic acid dehydrogenase, alkaline phosphatase, β-glucuronidase, catalase, lysozyme, acid phosphatase and leucine aminopeptidase, may have specific value in the diagnosis or localization of disorders of the urinary tract have been evaluated in the light of frequently conflicting reports. Attention has been called to the many factors which make accurate assay of enzymes in urine and the interpretation of results difficult. The results of our own studies of urinary lactic acid dehydrogenase and alkaline phosphatase are reported. These studies include groups of patients with carcinoma of the kidney, bladder and prostate, with chronic pyelonephritis, chronic glomerulonephritis, essential hypertension, hypertension associated with renal parenchymal disease and patients who received kidney transplants. Initial optimism unfortunately appears to have been excessive in most instances. False negatives, lack of etiological specificity and wide day-to-day fluctuations constitute problems, and few studies have demonstrated an appreciable advantage over urinalysis. Although restricted areas of value may be suggested, at this time assay of urinary enzymes cannot be said to have an important place in clinical urology or nephrology; nevertheless, additional studies are indicated and may demonstrate such a place in the future.

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REFERENCES

1. AMADOR, E., ZIMMERMAN, T. S. AND WACKER, W. E. C.: *J. A. M. A.*, **185**: 769, 1963.
2. AMADOR, E., DORFMAN, L. E. AND WACKER, W. E. C.: *Ann. Intern. Med.*, **62**: 30, 1965.
3. AMELUNG, D., HORN, H. D. AND SCHRÖDER, E.: *Klin. Wschr.*, **36**: 963, 963, 1959.
4. APPERT, O.: *Urol. Int.*, **20**: 359, 1965.
5. BÖTTIGER, L. E., LINDSTEDT, S. AND VON SCHREEB, T.: *Acta Chir. Scand.*, **132**: 356, 1966.
6. BRENNER, B. M. AND GILBERT, V. E.: *Amer. J. Med. Sci.*, **245**: 31, 1963.
7. COLBERT, D. W., CARRERA, A. E. AND KITTREDGE, W. E.: *Invest. Urol.*, **3**: 445, 1966.
8. COLTORTI, M. *et al.*: *Rif. Med.*, **76**: 1313, 1962.
9. CROCKSON, R. A.: *Lancet*, **1**: 140, 1961.
10. DELIVELIOTIS, A. *et al.*: *Presse Méd.*, **74**: 17, 1966.
11. DORFMAN, L. E., AMADOR, E. AND WACKER, W. E. C.: *J. A. M. A.*, **184**: 1, 1963.
12. DUBACH, U. C. AND REDIGER, R.: *Urol. Int.*, **17**: 65, 1964.
13. DUBACH, U. C.: *Helv. Med. Acta*, **33**: 139, 1966.
14. EMANUELLI, G., FIORELLI, G. AND VERZETTI, G.: *Minerva Med.*, **57**: 1619, 1966.
15. EMERSON, P. AND MORGAN, M. N.: *Brit. J. Urol.*, **38**: 551, 1966.
16. FIORELLI, G., EMANUELLI, G. AND PERPIGNANO, G.: *Minerva Med.*, **57**: 1625, 1966.
17. GAULT, M. H. AND STEINER, G.: *Canad. Med. Ass. J.*, **93**: 1101, 1965.
18. GAULT, M. H. *et al.*: *Brit. J. Urol.*, **39**: 296, 1967.
19. GELDERMAN, A. H., GELBOIN, H. V. AND PEACOCK, A. C.: *J. Lab. Clin. Med.*, **65**: 132, 1965.
20. GLENERT, J. *et al.*: *Nord. Med.*, **76**: 1274, 1966.
21. GOLDBERG, W. M., CHAKRABARTI, S. AND FILIPICH, R.: *Canad. Med. Ass. J.*, **94**: 1264, 1966.
22. GÜTTLER, F. AND CLAUSEN, I.: *Enzym. Biol. Clin. (Basel)*, **5**: 55, 1965.
23. HOCHELLA, N. J. AND WEINHOUSE, S.: *Anal. Biochem.*, **13**: 322, 1965.
24. KENNY, M. AND RAFELSON, M. E., JR.: *Fed. Proc.*, **24**: 667, 1965 (abstract).
25. KERN, W. H. AND WEBSTER, W. W.: *Acta Cytol. (Balt.)*, **8**: 302, 1964.
26. KERN, W. H., WEBSTER, W. W. AND BALES, C. E.: *J. Urol.*, **96**: 551, 1966.
27. KISER, W. S. AND RIGGINS, R. S.: *Ibid.*, **96**: 559, 1966.
28. KLAUS, D.: *Klin. Wschr.*, **36**: 207, 1958.
29. KOO, G. C. G. *et al.*: *Surg. Forum*, **16**: 256, 1965.
30. LEE, D. A. *et al.*: *J. Urol.*, **95**: 77, 1966.
31. MACALALAG, E. V., JR. AND PROUT, G. R., JR.: *Ibid.*, **92**: 416, 1964.
32. MIRABILE, C. S., BOWERS, G. N., JR. AND BERLIN, B. B.: *Ibid.*, **95**: 79, 1966.
33. NÄNTÖ, V., KASANEN, A. AND LEHTONEN, A.: *Ann. Med. Intern. Fenn.*, **55**: 23, 1966.
34. NOSAL, T. *et al.*: *Clin. Chem.*, **12**: 542, 1966 (abstract).
35. PLUMMER, D. T. AND LEATHWOOD, P. D.: *Biochem. J.*, **103**: 172, 1967.
36. POJER, J., MOJZIS, A. AND TOVAREK, J.: *Rev. Franç. Etud. Clin. Biol.*, **5**: 919, 1960.
37. PROUT, G. R., JR., MACALALAG, E. V., JR. AND HUME, D. M.: *Surgery*, **56**: 283, 1964.
38. RAMKISSOON, R. A. *et al.*: *J. Urol.*, **91**: 603, 1964.
39. RIGGINS, R. S. AND KISER, W. S.: *Ibid.*, **90**: 594, 1963.
40. *Idem*: *Invest. Urol.*, **2**: 30, 1964.
41. ROSALKI, S. B. AND WILKINSON, J. H.: *Lancet*, **2**: 327, 1959.
42. SANTONI, G. AND AREZZI BOZA, E.: *Ann. Ostet. Ginec.*, **87**: 416, 1965.
43. SCHMIDT, J. D.: *J. Urol.*, **96**: 950, 1966.
44. *Idem*: *Invest. Urol.*, **3**: 405, 1966.
45. *Idem*: *Ibid.*, **4**: 103, 1966.
46. SCHMIDT, J. D. AND MURPHY, G. P.: *Ibid.*, **4**: 57, 1966.
47. SCHOENENBERGER, G. A. AND WACKER, W. E. C.: *Biochemistry (Wash.)*, **5**: 1375, 1966.
48. SCHWARTZ, M. K. AND GRABSTALD, H.: *Clin. Chem.*, **13**: 1092, 1967 (abstract).
49. WACKER, W. E. C. AND DORFMAN, L. E.: *J. A. M. A.*, **181**: 972, 1962.
50. WACKER, W. E. C., DORFMAN, L. E. AND AMADOR, E.: *Ibid.*, **188**: 671, 1964.
51. ALLEN H. AND SPELLBERG, M. A.: *Arch. Intern. Med. (Chicago)*, **120**: 667, 1967.
52. BURGEN, A. S. V.: *Lancet*, **1**: 329, 1947.
53. BUTTERWORTH, P. J. *et al.*: *Clin. Chim. Acta*, **11**: 212, 1965.
54. *Idem*: *Ibid.*, **11**: 220, 1965.
55. DUBACH, U. C. AND PADLINA, G.: *Klin. Wschr.*, **44**: 180, 1966.
56. GREENBERG, W. V. AND TEMPLE, T. E.: *Amer. J. Clin. Path.*, **48**: 133, 1967.
57. HILLIARD, S. D., O'DONNELL, J. F. AND SCHENKER, S.: *Clin. Chem.*, **11**: 570, 1965.
58. PASTERNACK, A.: *Scand. J. Clin. Lab. Invest.*, **16**: 145, 1964.
59. WALTERS, C. L.: *Enzymolgia*, **20**: 33, 1958.
60. APPERT, O. AND RICHTERICH, R.: *Urol. Int.*, **20**: 206, 1965.
61. BANK, N. AND BAILINE, S. H.: *New Eng. J. Med.*, **272**: 70, 1965.
62. BOYLAND, E., WALLACE, D. M. AND WILLIAMS, D. C.: *Brit. J. Urol.*, **27**: 11, 1955.
63. FRIPP, P. J.: *Brit. J. Cancer*, **19**: 330, 1965.
64. ROMANO, C. AND SORRENTINO, F.: *Urologia (Treviso)*, **23**: 1, 1961.
65. HAIJE, W. G. AND VAN DER WERF-MESSING, B. H. P.: *Brit. J. Cancer*, **16**: 570, 1962.
66. HRADEC, E., PETRIK, R. AND PEZLAROVÁ, J.: *J. Urol.*, **94**: 430, 1965.
67. HYGSTEDT, O. AND JAGENBURG, O. R.: *Scand. J. Clin. Lab. Invest.*, **17**: 565, 1965.
68. KALLET, H. A. AND LAPCO, L.: *J. Urol.*, **97**: 352, 1967.
69. MELICOW, M. M., USON, A. C. AND LIPTON, R.: *Ibid.*, **86**: 89, 1961.
70. PAUL, W., SCHAPIRO, A. AND GONICK, H.: *Enzym. Biol. Clin. (Basel)*, **8**: 47, 1967.
71. ROBERTS, A. P. *et al.*: *New Eng. J. Med.*, **276**: 1468, 1967.
72. SAPIRA, J. D. AND SHAPIRO, A. P.: *Amer. J. Med. Sci.*, **253**: 174, 1967.
73. SCHAPIRO, A., PAUL, W. AND GONICK, H.: *Enzym. Biol. Clin. (Basel)*, **8**: 135, 1967.
74. LEWIS, F. J. W. AND PLAICE, C. H. J.: *Brit. J. Cancer*, **14**: 106, 1960.
75. MATTEA, E. AND PIETRA, E.: *Tumori*, **45**: 86, 1959.
76. PISCATOR, M.: *Arch. Environ. Health (Chicago)*, **12**: 335, 1966.
77. BALAZS, T. AND ROEPKE, R. R.: *Proc. Soc. Exp. Biol. Med.*, **123**: 380, 1966.
78. HARRISON, J. F. *et al.*: *Lancet*, **1**: 371, 1968.
79. NOBLE, R. E. AND BRAINERD, H. D.: *J. Urol.*, **96**: 852, 1966.
80. NOBLE, R. E., NAJARIAN, J. S. AND BRAINERD, H. D.: *Proc. Soc. Exp. Biol. Med.*, **120**: 737, 1965.
81. PROCKOP, D. J. AND DAVIDSON, W. D.: *New Eng. J. Med.*, **270**: 269, 1964.
82. WILSON, A. T. AND HADLEY, W. P.: *J. Pediat.*, **36**: 45, 1950.
83. *Idem*: *Ibid.*, **36**: 199, 1950.
84. OSSERMAN, E. F. AND LAWLER, D. P.: *J. Exp. Med.*, **124**: 921, 1966.
85. DANIEL, O., KIND, P. R. N. AND KING, E. J.: *Brit. Med. J.*, **1**: 19, 1954.
86. DELORY, G. E. AND HETHERINGTON, M.: *Canad. J. Med. Sci.*, **30**: 1, 1952.
87. FERNANDEZ, R. *et al.*: *Invest. Urol.*, **2**: 328, 1965.
88. SCHOENFELD, M. R.: *J. A. M. A.*, **193**: 618, 1965.
89. SCOTT, W. W. AND HUGGINS, C.: *Endocrinology*, **30**: 107, 1942.
90. BRAUDE, A. I.: *J. Clin. Invest.*, **38**: 990, 1959 (abstract).
91. BRAUDE, A. I. AND BERKOWITZ, H.: *J. Lab. Clin. Med.*, **57**: 490, 1961.
92. BROMBERG-SZNEK, S. AND LORSKA, D.: *Pol. Arch. Med. Wewnet.*, **35**: 1325, 1965.
93. BROMBERG-SZNEK, S. *et al.*: *Presse Méd.*, **73**: 21, 1965.
94. DOUNCE, A. L., ROBERTS, E. AND WILLS, J. H.: Catalasuria as a sensitive test for uranium poisoning. *In*: Pharmacology and toxicology of uranium compounds, vol. 2, edited by C. Voegtlin and H. C. Hodge, McGraw-Hill Book Company, New York, 1949, p. 889. Cited in: Leading Article: *Lancet*, **1**: 133, 1968.
95. KINCAID-SMITH, P. *et al.*: *Lancet*, **2**: 61, 1964.
96. MONTGOMERIE, J. Z., KALMANSON, G. M. AND GUZE, L. B.: *Amer. J. Med. Sci.*, **251**: 184, 1966.
97. MOUTSOS, S. E., STEIN, H. AND SHAPIRO, A. P.: *J. Lab. Clin. Med.*, **59**: 847, 1962.
98. SHAPIRO, A. P. *et al.*: *Amer. J. Cardiol.*, **17**: 638, 1966.
99. VIRTANEN, S. AND KASANEN, A.: *Nord. Med.*, **70**: 1082, 1963.
100. ONO, T. AND ETO, K.: *Jap. J. Clin. Path.*, **13**: 679, 1965.
101. SANTONI, G. AND BELGERI, R.: *Ann. Ostet. Ginec.*, **84**: 718, 1962.
102. SANTONI, G., BELGERI, R. AND VARIATI, C. V.: *Ibid.*, **87**: 795, 1965.
103. GAMBILL, E. E. AND MASON, H. L.: *J. A. M. A.*, **186**: 24, 1963.
104. WEBSTER, P. D. AND ZIEVE, L.: *Postgrad. Med.*, **31**: A-18, June 1962.
105. NOTHMAN, M. M., PRATT, J. H. AND CALLOW, A. D.: *A.M.A. Arch. Intern. Med.*, **100**: 221, 1957.
106. Editorial: *Canad. Med. Ass. J.*, **87**: 1337, 1962.
107. Editorial: *J. A. M. A.*, **181**: 990, 1962.
108. Editorial: *New Eng. J. Med.*, **276**: 1498, 1967.
109. KING, J. S., JR. AND BOYCE, W. H.: High molecular weight substances in human urine, Charles C Thomas Publisher, Springfield, Ill., 1963, p. 62.
110. DOSSETOR, J. B. *et al.*: *Transplantation* **5**: 844, 1967.
111. MATTENHEIMER, H.: Personal communication.
112. MACLEOD, J. AND WROBLEWSKI, F.: *Proc. Soc. Exp. Biol. Med.*, **99**: 265, 1958.
113. MATTENHEIMER, H.: Der Aussagewert von Enzymbestimmungen im Urin, *In*: Aktuelle Probleme der klinischen Biochemie, vol. 1, edited by H. Aebi, H. Mattenheimer and F. W. Schmidt, Hans Huber, Bern, 1968, p. 355. In press.
114. *Idem*: Enzymology of kidney tissue, *In*: Current problems of clinical biochemistry, vol. 2, edited by H. Aebi, H. Mattenheimer and F. W. Schmidt, Hans Huber, Bern, 1968, p. 119. In press (English translation).
115. GAULT, M. H. AND DOSSETOR, J. B.: In preparation.
116. HAYSLETT, J. P., PERILLIE, P. E. AND FINCH, S. C.: *New Eng. J. Med.*, **279**: 506, 1968.